REMARKS and REQUEST FOR CONSIDERATION

Claims 1-22 are currently pending in the application. Claims 14-22 have been withdrawn by the Examiner as being drawn to a non-elected group. Claims 5-6 and 8-11 have been withdrawn by the Examiner as being drawn to the non elected species. Claims 1-4, 7, 12 and 13 are examined on the merits.

Claim 12 is newly amended. The amendment finds support in the specification and is discussed in the relevant sections below. No new matter is added.

Priority

Applicant acknowledges the granting of priority benefits to United Kingdom applications 0017376.5, 0022943.5, 0029872.9, 0029870.3, 0029871.1 and 0110885.1.

Claim Rejections-35 USC § 112, First Paragraph

Enablement

The Office Action states that Claims 1-4, 7, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, enablement, because "the specification, while being enabling for a crystal structure of the *Thermus thermophilus* 30S subunit having a resolution of 3.05 Å, does not reasonably provide enablement for any 30S subunit, or any 30S subunit having a resolution numerically less than about 3 Å".

With regard to the position that the specification is not enabling for any 30S subunit having a resolution numerically less than about 3 Å, the Office Action states that the instant specification discloses a 30S subunit having a resolution of 3.05 Å, but does not disclose a 30S subunit having a resolution that is numerically less than about 3Å.

Applicant traverses this aspect of the rejection on the grounds that the specification teaches how to make and use the claimed crystal structure. The specification discloses on page 11, line 9-13, that " ..crystals which resolve to a resolution of at least about 3Å.." are selected. The specification discloses on page 4 that " An advantageous feature of the structure is that it defracts beyond 3Å resolution." (emphasis added). This disclosure of a crystal of the *Thermus thermophilus* 30S ribosomal subunit that defracts beyond 3Å resolution clearly contrasts with the assertion in the Office Action that there is no disclosure of a 30S subunit having a resolution of one that is numerically less than about 3 Å.

However, while not acquiescing to the instant rejection, and solely for the purpose of advancing prosecution, Applicant has amended claim 12 so it recites, in part, "A crystal having a resolution of about 3 Å".

Applicant also traverses the position of the Office Action that the specification is not enabling for ANY 30S subunit. Applicant submits that the instant specification provides enabling support for a crystal of ANY PROCARYOTIC 30S subunit having the recited resolution.

The Office Action asserts that "It is noted that structure conservation is only one of many characteristics of organisms such as prokaryotes, which have been used for the classification of said organisms. It is well known in the art that other characteristics (not a comprehensive example) such as gram stain, growth conditions, and metabolic properties have been widely used for classifying organisms of different species".

However, Applicant notes that the specification is not applying the property of structural conservation of ribosomes for classification of species. In fact, the specification is applying the property of structural conservation of ribosomes of different species in terms of making crystals from prokarytoic species.

The Office action contends that "factors such as growth conditions and metabolic properties of an organism strongly determine the effort required to predictably crystallize a specific protein from said organism", and that "The difference in the protein-surrounding environment due to the proteins being from organisms of different species greatly determines whether said proteins could be predictably crystallized using the same method". The Office

Action asserts that "even with regions of structure essential for function being conserved , the difference in protein sequence due to said sequences from different species outside of the conserved regions greatly determines whether said proteins could be predictably crystallized using the same method".

Applicant notes that it appears that though it may be unpredictable to crystallize individual proteins for the reasons stated above in the office action, Applicant notes that a crystal of an individual protein is not being claimed. Rather a crystal of a 30S ribosomal subunit is being claimed. The office action does not state why the principles of unpredictability in crystallizing a protein would apply to the unpredictability of a 30S ribosomal subunit. Applicant notes that unlike an individual protein, ribosomes are abundant and also have a defined conserved structure. Therefore, it is not clear that these assertions regarding the unpredictability of crystallizing a protein even apply to the crystallization of a large unit as a 30S ribosomal subunit.

In contrast, Applicant contends that the citation of a high degree of conservation of ribosome structure between prokaryotes of different species alone does enable one of skill in the art to predictably practice the claimed invention. The instant specification discloses how to make and use a crystal of a 30S ribosomal subunit from any prokaryotic species as encompassed by the instant claims, as follows;

> "This methodology provides those of skill in the art a means to provide 30S crystals of T.thermophilus. The conservation of ribosome structure, particularly regions of structure essential for function, between prokaryotes, for example prokaryotes which are human pathogens, such as Staphylococcus spp, and the like, allows the structure herein to be useful in the provision of anti-bacterial agents in general. Thus, the structure may be used to solve 30S subunits by the technique of molecular replacement. In such a method, x-ray diffraction data are obtained from crystals of a 30S subunit from another species, e.g. a species of a bacteria pathogenic to humans. The coordinates of Table 1 may be used to find the orientation of the unknown molecule in the crystal, and electron density maps calculated. These maps can then be interpreted with the sequence of the species in question, and the coordinates of our 30S structure can be used to help and speed interpretation. In this way, the structure of our 30S facilitates the determination of structures of 30S subunits and whole ribosomes from other organisms.
>
> **Accordingly, the invention provides a method for the determination of the structure of a bacterial 30S from a species other than T. thermophilus.**" (emphasis added).

The Office Action also states that "protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in a high failure rate for proteins that are being crystallized. Therefore researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002)".

Again, Applicant notes that the above assertions apply to proteins, and it is not clear how these assertions of unpredictability apply to ribosomal subunits which are heterogeneous complexes comprising protein and RNA. Further, in contrast to researchers having trouble generating sufficient protein required for the crystallization process, generating sufficient prokaryotic ribosomes for crystallization has not historically been troublesome, due to their abundance in prokaryotic cells and due to the ease of ribosomal purification from prokaryotic cultures. In fact, Applicants note that the first crystallization of a ribosomal subunit was over twenty years ago (Yonath et al. (1980) Biochem Int. 1, 428-435. Further Applicant notes that ribosomal subunits from several different species have been crystallized, as evidenced by Clemons et al (J. Mol. Biol. (2001):310:827-843) (IDS) which includes publications by Cate et al., (1999), Ban et al., (1999), Clemons et al., (1999), and Tocilj et al., (1999). In view of the many instances of ribosomal subunit crystallization over the years, it does not appear that there is a high failure rate for crystallization of ribosomal subunits, absent evidence to the contrary. In fact, Clemons teaches on pages 834-835 that 30S subunit crystals diffract well and that "the crystal form of the 30S subunit mimics a ligand bound state, which is probably responsible for its conformational homogeneity and the resulting diffraction to high resolution".

In view of Applicant's arguments detailed above and in view of the specification's teaching of the applicability of the disclosed crystallization methods to 30S ribosomal subunit from any prokaryotic species, Applicant respectfully submits that the office action has not met its burden in demonstrating that the specification is not enabling for the crystallization of any prokaryotic 30S ribosomal subunit.

In view of the amendment to claim 12, and in view of the above mentioned arguments, Applicant respectfully requests reconsideration and withdrawal of this aspect of the rejection on

the grounds that the instant specification clearly discloses how to make and use a crystal of a prokaryotic 30S subunit as instantly claimed.

Written Description

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant respectfully traverses the rejection on the grounds that the specification contains support for the limitation of a "crystal of a 30S ribosomal subunit having a resolution numerically less than about 3Å". Attention is directed to page 4, lines 10-14 of the instant specification, wherein the following is disclosed:

"In a first aspect, the present invention provides a crystal of the *Thermus thermophilus* 30S subunit having a tetragonal space group $P4_12_12$ with unit cell dimensions of a = 401.375 Å, b = 401.375 Å, c=175.887 Å, or more generally about a =401.4 Å, b=401.4 Å, c=175.9 Å, but more preferably a =401.4 ± about 4.0 Å, b=401.4 ± about 4.0 Å, c=175.9 ± about 5.0 Å. ***An advantageous feature of the structure is that it defracts beyond 3Å resolution***." (emphasis added).

However, while not necessarily acquiescing to the new matter rejection of claim 3, in the sole interest of advancing prosecution, Applicant has currently amended claim 3 to recite "A crystal of a prokaryote 30S ribosomal subunit .....having a resolution about 3 Å.". In view of this amendment and its support throughout the specification, including pages 4 and 11 as described above, and Table 1, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

Claims 1-4, 7, 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 09/904,779, in view of Ramakrishnan et al.

Upon indication of allowable subject matter, a terminal disclaimer will be filed.

Conclusion

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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